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PATENT APPLICATION
Attorney's Docket No.: 2719.2001-000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Glenn McGall

Application No.: 09/659,599 Group: 1635

Filed: September 11, 2000 Examiner: Epps-Ford, Janet L.

Confirmation No.: 4766

For: SYNTHESIS OF OLIGONUCLEOTIDE ARRAYS USING
PHOTOCLEAVABLE PROTECTING GROUPS

CERTIFICATE OF MAILING OR TRANSMISSION	
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DECLARATION OF GLENN H. MCGALL, PH.D. UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Glenn H. McGall, Ph.D., of Palo Alto, CA, declare and state that:

1. I am the inventor of U.S. Application No. 09/659,599, filed on behalf of Affymetrix, Inc., 3380 Central Expressway, Santa Clara, California, 95051.

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2. I have thoroughly studied the above-identified application and the Office Actions mailed from the Patent Office on April 9, 2003, November 17, 2003 and April 20, 2004, where claims 1 to 23 and 30 to 38 are rejected as being unpatentable over McGall *et al.* (U.S. Patent No. 5,412,087; hereinafter "the '087 Patent") in view of McGall *et al.* (WO 98/39348 A1; hereinafter "the '348 Publication"). I am the first-named inventor for both of these cited references.

3. From my education, experience and supervision of junior scientists in my laboratory at Affymetrix, I am readily familiar with the level of ordinary skill in the art as it pertains to the above references and the Examiner's rejection. A copy of my curriculum vitae is attached as Appendix A.

4. I am informed that the Examiner takes the position that nitro-benzylic based photoprotective cleavable group would be obvious to one of ordinary skill in the art based on the '087 patent in view of the '348 publication. I further understand that the Examiner extends this position to non-benzylic, multi-aromatic ring structures based on these publications.

5. I have carefully studied the Examiner's rejections and in particular all of the cited references and passages thereof referred to by the Examiner. Based on my review and my scientific training and experience with photosensitive protective groups, I respectfully disagree with the Examiner that a person of ordinary skill would find the instantly claimed invention to be obvious.

6. Furthermore, based on the research of my group here at Affymetrix, I have specific scientific findings showing that the Examiner's conclusions in regard to obviousness are incorrect. In particular my group and I have performed extensive research on photoprotective cleavable groups. These are also called photosensitive protecting groups. The terms are synonymous. We have studied many such groups both directly, looking at the wavelength of light the groups can be cleaved with, the photospeed of the groups (i.e., how quickly the group comes off after exposure to light) and whether the groups generated undesirable side products upon exposure to light and indirectly, fabricating nucleic acid arrays using the groups. The results of our work are disclosed in numerous patents and in peer-reviewed journals. (See, e.g., U.S. Patent Nos. 5,599,695, 5,831,070, 5,959,098, 6,150,147, 6,239,273 and 6,307,042.).

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7. In using a photosensitive protective group to fabricate a nucleic acid array: there are several crucial features in regard to the group. The photosensitive group must have a reasonably high photospeed to allow efficient removal of the group and subsequent exposure of the hydroxyl group.

8. The photosensitive group must be cleavable at wavelengths of light of approximately 365 nm. As shown in Figure 6 (page 814) of the attached Exhibit B (C. Kielbassa *et al.*, "Wavelength Dependence of Oxidative DNA Damage Induced By UV and Visible Light", *Carcinogenesis* 18:811-816 (1997)), UV light of wavelengths shorter than 365 nm irrevocably damage the growing oligonucleotide strand. See also Cadet, J.; Vigny, P. in *Bioorganic Photochemistry, Vol. 1*, Morrison, H., Ed., Wiley: New York, 1990; pp. 1-272 (copy not enclosed) regarding DNA damage caused by UV light. For example, T nucleotides undergo dimerization. It is also known to those of skill in the art that cleavage of the DNA strand may result from exposure to very short wavelength UV. Such damage is completely undesirable because the damaged DNA is unable to undergo base pairing.

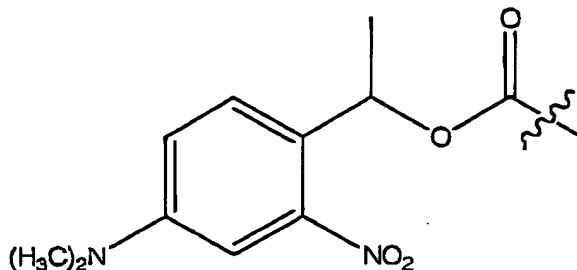
9. Finally, the photosensitive group must not produce undesirable photochemical byproducts which, for example, prevent subsequent reaction of the exposed group to another nucleotide monomer.

10. The notion that that all nitrobenzylic compounds are obvious photosensitive protecting groups is incorrect. My research group has studied a number of putative nitrobenzylic photosensitive protecting groups, but found them to be cleavable at wavelengths of light too low to be useful in DNA synthesis. For example, the nitro-benzyl derivative NBOC, which is shown in Table 1, col. 8 of the '087 Patent, undergoes photolysis at high rates at 305 nm, but is negligibly cleavable at 365 nm. Repeated exposure of oligonucleotide strands of DNA to UV light having a wavelength of 305 nm would result in substantially damaged strands of oligonucleotides. For example, photochemical modification of the growing DNA molecules, such as pyrimidine dimerization, would occur, resulting in DNA strands unable to undergo normal Watson-Crick base pairing.

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11. Our group recently fabricated another nitrobenzylic group as part of our ongoing research efforts. Although the group has significant absorption at 365 nm (generally a good indicator that it will cleave at that wavelength) the molecule (shown below) is not photocleavable at all with 365 nm wavelength light:



12. Nitrobenzylic compounds are preferred photosensitive protective groups as is said in the '087 patent. However, as seen from the evidence above, the '087 Patent and the '348 Publication do not render every nitrobenzylic compound (or multi-ring compounds having a nitro group) obvious as desirable photosensitive photoprotecting groups.

I hereby acknowledge that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Glenn H. McGall, Ph.D.

Date